PHARMACEUTICAL PREPARATION FOR THE ORAL CAVITY

The invention relates to a pharmaceutical preparation for the oral cavity consisting of an aqueous solution, buffered to a physiological pH, provided with antiinflammatory and analgesic activity, particularly suitable for spraying into the oral cavity by means of a suitable dosing pump.

For around a decade now, the incidence of generalised inflammatory conditions of the throat, mouth and gums has been on the increase, especially during the winter. These very troublesome conditions are not generally attributable to a specific cause, but may arise due to various external factors, such as for example sudden changes in ambient temperature, irritant or toxic substances contained in the air or in polluted environments, direct or indirect inhalation of cigarette smoke, or internal factors, such as for example slight infections with viruses, echoviruses, macro viruses or bacteria or, as frequently occurs, due to the simultaneous presence of one or more of these irritants. The resultant clinical picture is thus highly complex, with inflammation and pain predominating among the many symptoms. Since it is consequently not possible to combat each of these various causes individually with a specific, targeted

treatment, the only possible therapeutic strategy is to eliminate the troublesome symptoms of these conditions as effectively as possible, primarily by countering the inflammation or the congestion of the throat, mouth and gums, while simultaneously also alleviating or eliminating the troublesome pain.

The products usable to treat this complex clinical picture which are currently commercially available may in general terms be divided into two categories.

The first of these consists of a range of products based on natural substances or extracts, such as propolis, mixtures of honey and wild rose, eugenol and others. The second category, on the other hand, comprises medicinal preparations containing one or more pharmaceutical active ingredients which must combine efficacy with an optimum safety and tolerability profile. These medicinal preparations are generally classified by the European health authorities as "self-medication products", which the patient may accordingly request on his/her own initiative or after consulting a doctor, pharmacist or any other health professional or in response to advertising messages.

These pharmaceutical products, although subject to prior approval as medicines by the health regulatory

authorities (since they contain one or more active ingredients) and thus frequently being sold only in pharmacies (the specific legislation may vary from country to country), may be freely sold directly to any patient requesting them without there being any need to submit a doctor's prescription. This explains the alternative names for these medicines which are also known as "freely sold products" or "over-the-counter products".

Taking due account of the above, a medicinal product for self medication to be used as an antiinflammatory and analgesic for spraying into/onto the mouth, throat and gums must necessarily meet various ideal requirements, including:

(a) satisfactory antiinflammatory and analgesic activity, both for reducing congestion and for alleviating the associated pain; the active ingredient must furthermore be homogeneously dissolved in the solution so that it can be sprayed uniformly into the oral cavity;

(b) the solution must be pharmaceutically stable and the active and auxiliary ingredients must accordingly not react with one another;

(c) the solution must be biologically acceptable to the oral mucosa, and thus neither excessively acidic, so as

not to attack the dentine, nor excessively basic, so as not to exacerbate the irritation;

(d) provision of a mild disinfectant action to protect the mouth and pharynx from any bacterial and viral attack;

(e) have a preservative action to protect the solution from bacterial contamination and proliferation during production and subsequent use;

(f) be organoleptically acceptable since it is intended for an organ which is particularly delicate and sensitive to unpleasant flavours and odours.

An ideal aqueous solution must thus remain stable for a certain period of time, being clear and transparent without precipitates and contaminants. It will thus be necessary to avoid certain incompatibilities, such as using parabens with a pH greater than 8.0, introducing a highly reactive inorganic substance, such as for example potassium bicarbonate, into the composition, using edetic acid and some of the salts thereof which attack the calcium of the dentine ("Handbook of Pharmaceutical Excipients", 4th edition, 2003, American Pharmaceutical Association, page 226, paragraph 14, Safety) or using unstable colorants in order to avoid loss of colour during ageing and so on.

At present, there is no pharmaceutical composition available which is capable of combining all the ideal features listed above. Indeed, the formulations which may be found in the literature or those already on the market (trade names are deliberately not stated so as not to give rise to any unjustified accusation of unfair competition) lack the majority of the properties listed above.

The new generation nonsteroidal antiinflammatories, such as for example COX-2 inhibitors (celecoxib, rofecoxib and others), cannot be used topically due their mechanism of action. Other first generation nonsteroidal antiinflammatory drugs (NSAIDs), on the other hand, cannot be used due to the high concentration which is required (ibuprofen, tiaprofenic acid), or due to their known instability in water (acetylsalicylic acid), or also due to their sparing solubility (piroxicam, tenoxicam). Still others are known to have sensitising potential (diflunisal, zomepirac), which makes topical use thereof inadvisable.

Of the remaining active ingredients, some (naproxen and etodolac) exhibit a predominant antiinflammatory activity and inadequate analgesic activity, while others conversely exhibit a predominant analgesic

activity (ketorolac) and little antiinflammatory activity. Some products already on the market occasionally exhibit a pH of greater than 8.0 and are thus not physiologically compatible with the mucosa and furthermore result in harmful dysmicrobism of the oral cavity's saprophytic flora. The physiological pH of the mouth is in fact between 6.7 and 7.5.

Given that no pharmaceutical composition which is described in the literature or is commercially available is capable of meeting the requirements listed above, there is accordingly an urgent need to fill this gap with a pharmaceutical preparation which combines the features listed above.

After various studies and experimental trials, a pharmaceutical preparation combining said features has now surprisingly been found, said preparation containing:

(a) a nonsteroidal antiinflammatory drug (NSAID) with analgesic activity;

(b) a biologically compatible buffering organic amine;

(c) a buffered pH of between 6.5 and 8.0, preferably of between 7.0 and 7.5,

(d) pharmaceutical grade water.

The solution buffered in this manner may furthermore contain:

(e) a mild disinfectant

(f) one or more preservatives

(g) other auxiliary ingredients.

The invention thus also relates to the pharmaceutical dosage form based on the solution defined above. Said solution may furthermore be distributed in a container with volume ranging from 10 to 100 ml.

The invention thus also relates to the complete packaged form of the solution defined above, which consists of a container, which encloses the buffered solution, provided with a dosing pump and a suitable distributor for spraying the solution directly into the oral cavity.

The invention also relates to a process for the production of the solution, as defined above, the apportioning thereof into the final packaging ready for distribution, sale and use by the patient, said process comprising the following sequence of operations:

(1) dissolution of one or more preservatives in more than 50% of the total necessary quantity of water, which has previously been heated to approx. 80°C, and subsequent cooling of the

solution to ambient temperature of approx. 25°C;

(2) dissolution of the selected NSAID in water or better in a mixture of equal proportions of water/ethyl alcohol, with immediate buffering with the selected organic amine to the specified pH;

(3) addition of the other ingredients to the mixture (1);

(4) pouring the solution (2) gradually into the solution (3) and mixing sufficiently;

(5) making up to volume (or weight) with water and, if necessary, adjusting the pH to the specified value with the organic amine;

(6) the buffered solution is apportioned into the container, which is sealed with the dosing pump; the suitable distributor is fitted onto the pump and the system is then packaged into its box with the patient information leaflet.

The invention will now be illustrated in greater detail in the following description.

The first object of the invention is accordingly to provide a pharmaceutical preparation consisting of an aqueous solution which contains:

(A) a nonsteroidal antiinflammatory drug (NSAID) in a sufficient quantity in the unit dose to effect a balanced antiinflammatory and analgesic action. The best results have been obtained when the NSAIDs selected for this purpose are flurbiprofen and diclofenac. Flurbiprofen in particular exhibits an high therapeutic index. Flurbiprofen may be employed as a racemate (or racemic mixture) or as one of its enantiomers, namely, (R)-(-) flurbiprofen or (S)-(+) flurbiprofen, and more particularly (R)-(-)flurbiprofen. The selected NSAID is used alone in the solution in a range of concentration within which the optimum concentration has been determined for the type of indication, as shown in Table 1 below:

Table 1

NSAID	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)	Optimum concentration in mg/ml (% wt./vol.)
Flurbiprofen	1.5 (0.15%)	8.0 (0.8%)	2.5 (0.25%)
Diclofenac	0.5 (0.05%)	1.5 (0.15%)	0.74 (0.074%)

(B) a biologically compatible organic amine with pronounced buffering properties, present alone or as a

mixture, with the buffering amino group in free or partially substituted form, used in a sufficient quantity to maintain the pH of the solution within a specified range close to the physiological pH of the oral cavity. The most surprising results have been obtained when the selected buffering organic amine consists of D-glucamine, meglumine, or trometamol (tris buffer). Meglumine in particular, having a methyl monosubstituted amino group and thus a weaker buffering action, as has also been described in the literature (Merck Index 13th ed. / meglumine 1.0% = pH 10.5 and trometamol 0.1% = pH 10.1), is more readily suitable to obtain the desired pH. Trometamol, on the other hand, is also highly advisable, being described in the classic, most reliable textbooks of chemical pharmacology as the only "non-toxic amine" to act as a "biological buffer".

The desired buffering action is generally obtained at a concentration which varies for each buffering organic amine and is stated in Table 2 below.

Table 2

Buffering substance	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)
Glucamine	0.35 (0.035%)	1.12 (0.112%)
Meglumine	0.40 (0.04%)	2.4 (0.24%)
Trometamol(tris buffer)	0.10 (0.01%)	0.75 (0.075%)

(C) the pH of the solution is within a range between 6.5 and 8.0, preferably between 7.0 and 7.5. This pH value is accordingly obtained by buffering the specified quantity of the selected NSAID with the (mono- or disubstituted) buffering organic amine in the quantity required to obtain a biocompatible pH as close as possible to the physiological pH of the mouth, which lies between 6.7 and 7.5. This pH range is furthermore particularly suitable for avoiding any modification of the physiological balance of the saprophytic bacterial flora of the oral cavity.

(D) pharmaceutical grade water, such as purified or twice-distilled water, of the quality specified in the usual pharmacopoeias.

The second object of the pharmaceutical preparation of the invention is to provide a buffered solution which exhibits further improvements in terms of its pharmaceutical, technical and organoleptic properties.

Thus, if there is an objective requirement to have a buffered solution which is also suitable for combatting superficial infective conditions arising from bacterial or viral infections, there is also an objective requirement to provide:

(E) a mild surface disinfectant which is biologically and pharmaceutically compatible with topical use and is selected from among those conventionally used for similar topical indications and applications in a quantity which is familiar to the person skilled in the art. This substance must furthermore be chemically compatible with the other ingredients of the solution and with the dispensing system used. The disinfectant which is typically selected consists of cetylpyridinium chloride or of glycyrrhizic acid or the ammonium or dipotassium salts thereof, the antibacterial and antiviral properties of which have already been

thoroughly described in the literature. The disinfectant substance is present alone in the solution, in a sufficient quantity to exert a specific antibacterial and antiviral action. Besides, glycyrrhizic acid, or the ammonium or dipotassium salt thereof, also exhibits a considerable sweet flavour approx. 50 times more powerful than sucrose.

The mild disinfectant selected is used alone in the buffered solution in a variable quantity in a range within which the optimum concentration has also been determined, as shown in Table 3 below:

Table 3

Mild disinfectant	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)	Optimum concentration in mg/ml (% wt./vol.)
Cetylpyridinium chloride	1.0 (0.01%)	6.0 (0.6%)	5.0 (0.5%)
Glycyrrhizic acid or salts thereof	0.8 (0.08%)	1.2 (0.12%)	1.0 (0.1%)

The buffered solution of the invention is furthermore generally packaged for preservation, distribution and

subsequent use in a multidose container, equipped with a suitable pressure dosing pump which makes it possible to spray the solution uniformly into/onto the throat, mouth and gums. In this case, however, there is a real risk that, due to the reduction in internal pressure arising from repeated use of the pump, contaminated air will enter the container from outside causing accidental contamination or the proliferation of bacterial colonies in the solution itself.

Thus, unless a more advanced pump is used, which is already commercially available, although at higher cost, and is equipped with a suitable filtration system which sterilises the air entering the container to compensate the reduction in internal pressure, the buffered solution must also contain:

(F) a preservative substance, or a mixture thereof, which is selected from among those conventionally used and in the quantity familiar to the person skilled in the art, in order to achieve sufficient microbiological control of the solution, and is moreover compatible with the topical mode of administration and also from the chemical standpoint not only with the other ingredients of the solution, but also with the components of the multidose system used. The typical preservatives

selected comprise not only conventional parabens, such as methyl p-hydroxybenzoate or propyl p-hydroxybenzoate, each of which alone or in combination, but in particular also disodium calcium edetate (i.e. not the simple disodium salt which is capable of attacking the calcium in tooth enamel), or finally sodium benzoate.

The selected preservative is used in the buffered solution at the appropriate concentration to prevent bacterial contamination and proliferation, as shown in Table 4 below:

Table 4

Preservative substance	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)
Methyl p-hydroxybenzoate	0.25 (0.025%)	1.15 (0.115%)
Propyl p-hydroxybenzoate	0.03 (0.003%)	0.15 (0.015%)
Disodium calcium edetate	0.1 (0.01%)	1.0 (0.1%)
Sodium benzoate	0.2 (0.02%)	5.0 (0.5%)

A mixture of two or more of the above preservatives may also be employed. Preferably, each component of the

mixture is present in an amount within the assigned limits of Table 4 above.

Finally, in order to improve the final technical, pharmaceutical and organoleptic properties of the buffered solution, bearing in mind that flavour is a non-negligible factor in a product which is intended to be sprayed into the oral cavity, it is necessary for the pharmaceutical preparation of the invention to be improved from the technical and organoleptic standpoint by the addition of other auxiliary ingredients, as indicated below.

(G) The nature, the quality and the concentration of each individual auxiliary ingredient varies from case to case depending on the starting buffered solution and on the final properties of the preparation which it is desired to obtain.

With regard to the quality of an individual auxiliary ingredient, a person skilled in the art will certainly be capable of selecting that which complies with the quality specifications stated in the specific monograph published in one of the main pharmacopoeias (Eur. Ph., USP, JP, FU, BP). In the absence of a specific monograph, the person skilled in the art will be able to select the auxiliary ingredient with properties

which comply as well as possible with those stated in specialist publications, such as for example "Remington: The Science and Practice of Pharmacy", 20th Edition, editors A.R. Gennaro et al., University of the Sciences in Philadelphia College or "Handbook of Pharmaceutical Excipients", 4th Edition, 2003, American Pharmaceutical Association.

The following Examples provide purely indicative examples of specific auxiliary ingredients and the associated optimum concentrations for each buffered solution illustrated in the Examples themselves.

The preferred auxiliary ingredients which are selected and thus also the concentration thereof are accordingly not binding for each buffered solution and do not limit the invention, it being possible to replace each of them suitably with another similar ingredient while still obtaining a result which is comparable overall with that of the invention itself.

Nevertheless, with regard to the quality and quantity thereof stated in the Examples, these ingredients are the result of careful optimisation which was not carried out casually but also involved an inventive step. The preferred auxiliary ingredients for the following Examples are stated below:

- glycerol (viscosity agent)
- sorbitol, xylitol (sweetening agent)
- ethyl alcohol (fluidising agent)
- castor oil 40 polyethoxylate (thickening agent)
- saccharin sodium, acesulfame potassium (sweeteners)
- mint essence, natural mint flavour, natural peach flavour (natural essences or flavours)
- patent blue V-E131, E-124 (colours).

The solution according to the invention is prepared in the above-stated sequence using the methods and machinery conventionally used in the pharmaceutical sector, but this is neither mandatory nor does it limit the invention itself. Indeed, adjustments remain possible with regard to the specific formulation used, the overall volume of the batch to be prepared, while nevertheless obtaining a result which is comparable overall with that of the invention itself.

The solution is generally packaged for preservation, distribution, sale and use in a suitable container provided with a dosing pump with an associated distributor, in such a manner that it may readily be sprayed directly into/onto the mouth, throat and gums. In particular, the solution is preferably packaged in a multidose container equipped with a pressure operating

pump, fitted with a dispensing erogator (of variable type and shape) which enables uniform spraying of the solution within the oral cavity.

In general, the volume of solution sprayed for each dose varies as a function of the concentration of the active ingredient, but for the formulations of the Examples, the ideal volume to be sprayed for each dose ranges from 100 to 300 microlitres, with an amount of 200 microlitres preferably being sprayed for each unit dose.

The pharmaceutical preparation of the invention is useful for the topical treatment of inflammatory conditions of the mouth, throat and gums with accompanying pain and, where the composition also contains a mild disinfectant, also for combatting the condition brought about by the bacterial and viral component which is often associated therewith. The preparation has thus also proved useful in reducing the inflammation/congestion and associated pain of the mucosa of the oral cavity. Another important aspect of the invention is the use of xylitol as a sweetening agent which, while exhibiting specific bacteriostatic and bactericidal effects, is not utilised by the microorganisms and does not promote dental plaque with its associated cariogenic effects.

Examples of typical buffered solutions of the invention are presented below in tabular form in order to make the individual details more readily discernible.

These Examples are provided with the aim of better illustrating the invention and thus do not constitute any limitation of the invention itself, it being obvious that the spirit and scope of the invention also include any other modifications which are obvious to the person skilled in the art.

EXAMPLES 1 TO 3

INGREDIENT	TYPE		EXAMPLES 1 TO 3 (mg/ml)		
			1	2	3
Flurbiprofen	A	mg	2.50	2.50	2.50
Diclofenac	A	mg	---	---	---
Glucamine to make up to pH (C)	B	mg	---	---	---
Meglumine to make up to pH (C)	B	mg	÷ 2.10	÷ 2.15	÷ 0.70
Trometamol to make up to pH (C)	B	mg	---	---	÷ 0.40
pH	C		7.10	7.30	7.20
Cetylpyridinium chloride	E	mg	---	---	---
Glycyrrhizic acid	E	mg	---	---	---
Methyl p-hydroxybenzoate	F	mg	1.00	---	1.00
Propyl p-hydroxybenzoate	F	mg	0.20	---	0.20
Disodium calcium edetate	F	mg	---	0.50	---
Sodium benzoate	F	mg	---	---	---
Glycerol	G	mg	100.00	100.00	100.00
Sorbitol	G	mg	70.00	70.00	70.00
Xylitol	G	mg	---	---	---
Ethyl alcohol (96%)	G	mg	100.00	100.00	100.00
Hydrogenated castor oil 40 polyethoxylate	G	mg	24.00	24.00	24.00
Saccharin sodium	G	mg	1.50	1.50	1.50
Acesulfame potassium	G	mg	---	---	---
Mint essence	G	mg	6.00	6.00	6.00
Natural mint flavour	G	mg	---	---	---
Natural peach flavour	G	mg	---	---	---
Patent blue V-E131	G	mg	---	0.006	---
Colour E124	G	mg	---	---	---
Purified water up to volume	D	ml	1.00	1.00	1.00

(A) = Active ingredient
(B) = Buffering organic amine
(C) = pH
(D) = Water (pharmaceutical grade)
(E) = Disinfectant
(F) = Preservative

(G) = Auxiliary ingredient

The following compositions are prepared as described in the method of the subsequent Example.

EXAMPLES 4 TO 7

INGREDIENT	TYPE		EXAMPLES 4 TO 7 (mg/ml)			
			4	5	6	7
Flurbiprofen	A	mg	2.50	2.50	---	---
Diclofenac	A	mg	---	---	0.74	0.74
Glucamine to make up to pH (C)	B	mg	---	÷ 1.00	---	---
Meglumine to make up to pH (C)	B	mg	÷ 2.30	---	÷ 0.55	---
Trometamol to make up to pH (C)	B	mg	---	---	---	÷ 0.16
pH	C		7.00	7.50	7.40	7.30
Cetylpyridinium chloride	E	mg	5.00	---	---	---
Glycyrrhizic acid	E	mg	---	1.00	---	1.00
Methyl p-hydroxybenzoate	F	mg	1.00	---	---	---
Propyl p-hydroxybenzoate	F	mg	0.20	---	---	---
Disodium calcium edetate	F	mg	---	0.50	0.50	0.50
Sodium benzoate	F	mg	---	---	1.00	1.00
Glycerol	G	mg	100.00	100.00	---	---
Sorbitol	G	mg	70.00	70.00	70.00	70.00
Xylitol	G	mg	---	---	---	---
Ethyl alcohol (96%)	G	mg	100.00	100.00	---	---
Hydrogenated castor oil 40 polyethoxylate	G	mg	24.00	24.00	---	---
Saccharin sodium	G	mg	1.50	1.50	---	---
Acesulfame potassium	G	mg	---	---	1.50	1.50
Mint essence	G	mg	6.00	6.00	---	---
Natural mint flavour	G	mg	---	---	10.00	12.00
Natural peach flavour	G	mg	---	---	10.00	12.00
Patent blue V-E131	G	mg	---	0.006	---	---
Colour E124	G	mg	---	---	---	0.006
Purified water up to volume	D	ml	1.00	1.00	1.00	1.00

(A) = Active ingredient

(B) = Buffering organic amine
(C) = pH
(D) = Water (pharmaceutical grade)
(E) = Disinfectant
(F) = Preservative
(G) = Auxiliary ingredient

The following compositions are prepared as described in the method of the subsequent Example.

EXAMPLES 8 TO 10

INGREDIENT	TYPE		EXAMPLES 8 TO 10 (mg/ml)		
			8	9	10
Flurbiprofen	A	mg	2.50	2.50	---
Diclofenac	A	mg	---	---	0.74
Glucamine to make up to pH (C)	B	mg	---	---	---
Meglumine to make up to pH (C)	B	mg	÷ 2.10	---	÷ 0.55
Trometamol to make up to pH (C)	B	mg	---	÷ 0.70	---
pH	C		7.10	7.40	7.20
Cetylpyridinium chloride	E	mg	---	---	---
Glycyrrhizic acid	E	mg	---	---	---
Methyl p-hydroxybenzoate	F	mg	1.00	1.00	---
Propyl p-hydroxybenzoate	F	mg	0.20	0.20	---
Disodium calcium edetate	F	mg	---	---	0.50
Sodium benzoate	F	mg	---	---	1.00
Glycerol	G	mg	100.00	100.00	---
Sorbitol	G	mg	---	---	---
Xylitol	G	mg	70.00	70.00	70.00
Ethyl alcohol (96%)	G	mg	100.00	100.00	---
Hydrogenated castor oil 40 polyethoxylate	G	mg	24.00	24.00	---
Saccharin sodium	G	mg	1.50	1.50	---
Acesulfame potassium	G	mg	---	---	1.50
Mint essence	G	mg	6.00	6.00	---
Natural mint flavour	G	mg	---	---	10.00
Natural peach flavour	G	mg	---	---	10.00
Patent blue V-E131	G	mg	---	0.006	---
Colour E124	G	mg	---	---	---
Purified water up to volume	D	ml	1.00	1.00	1.00

(A) = Active ingredient
(B) = Buffering organic amine

(C) = pH
(D) = Water (pharmaceutical grade)
(E) = Disinfectant
(F) = Preservative
(G) = Auxiliary ingredient

The following compositions are prepared as described in the method of the subsequent Example.

Example 11

Preparation of 2000 vials containing 15 ml of solution for spraying according to the composition of Example 1.

Production batch formula for 2000 vials containing 15 ml of solution for spraying:

Ingredient	15 ml vial		Total	
Flurbiprofen	37.50	mg	75.00	g
Meglumine to make up to pH (C)	÷ 31.50	mg	÷ 63.00	g
pH	7.10		7.10	
Methyl p-hydroxybenzoate	15.00	mg	30.00	g
Propyl p-hydroxybenzoate	3.00	mg	6.00	g
Glycerol	1.50	g	3.00	kg
Sorbitol	1.05	g	2.10	kg
Ethyl alcohol (96%)	1.50	g	3.10	kg
Hydrogenated castor oil 40 polyethoxylate	360.00	mg	720.00	g
Saccharin sodium	22.50	mg	45.00	g
Mint essence	90.00	mg	180.00	g
Purified water up to volume	15.00	ml	30.00	l

Phase 1 - Solution A

20 litres of purified water are placed in a suitable stainless steel dissolver and adjusted to approx. 80°C. Completely dissolve 30.0 g of methyl p-hydroxybenzoate and 6.0 g of propyl p-hydroxybenzoate. Cool the solution to ambient temperature (25°C).

Phase 2 - Solution B

3 litres of water and 3.0 kg of 96% ethyl alcohol are mixed in a suitable stainless steel container at approx. 30°C. Then add 75.0 g of flurbiprofen and buffer to pH 7.1 with meglumine (approx. 63 g).

Phase 3 - Solution C

While continuously stirring solution A, add the other ingredients: 3.0 kg of glycerol, 2.1 kg of sorbitol, 720.0 g of hydrogenated castor oil 40 polyethoxylate, 45.0 g of saccharin sodium and 180.0 g of mint essence. Stir until dissolution is complete.

Phase 4 - Buffered solution

Adjust the volume to 30 litres by adding purified water and check the pH. If necessary, buffer the pH to the desired value of 7.1 by adding meglumine.

The buffered solution is then apportioned into the vials which are sealed with the dosing pump equipped with a dispensing erogator. The system is then packaged in a suitable box. In this manner, 1865 vials each of 15 ml are obtained.